CHAPTER 15

Cortico-cortical networks and cortico-subcortical loops for the higher control of eye movements

J.C. Lynch1,* and J.-R. Tian2

1Departments of Anatomy, Ophthalmology, and Neurology, University of Mississippi Medical Center, 2500 N. State Street, Jackson, MS 39216, USA
2Jules Stein Eye Institute, UCLA Medical Center, 3-310 DSERC, 100 Stein Plaza, Los Angeles, CA 90095, USA

Abstract: There are multiple distinct regions, or eye fields, in the cerebral cortex that contribute directly to the initiation and control of voluntary eye movements. We concentrate on six of these: the frontal eye field, parietal eye field, supplementary eye field, middle superior temporal area, prefrontal eye field, and area 7 m (precuneus in humans). In each of these regions: (1) there is neural activity closely related to eye movements; (2) electrical microstimulation produces or modifies eye movements; (3) surgical lesions or chemical inactivation impairs eye movements; (4) there are direct neural projections to major structures in the brainstem oculomotor system; and (5) increased activity is observed during eye movement tasks in functional magnetic resonance imaging or positron emission tomography experiments in humans. Each of these eye fields is reciprocally connected with the other eye fields, and each receives visual information directly from visual association cortex. Each eye field has distinct subregions that are concerned with either saccadic or pursuit eye movements. The saccadic subregions are preferentially interconnected with other saccade subregions and the pursuit subregions are preferentially interconnected with other pursuit subregions. Current evidence strongly supports the proposal that there are parallel cortico-cortical networks that control purposeful saccadic and pursuit eye movements, and that the activity in those networks is modulated by feedback information, via the thalamus, from the superior colliculus, basal ganglia, and cerebellum.

Introduction and overview

The highest level of oculomotor control resides in the cerebral cortex. It is there that sensory input is combined with internally stored neural information to produce a representation of an individual’s surroundings. It is at the cortical level that potential targets for gaze are analyzed and selected and a decision is made about whether or not to execute an eye movement from one target to another, or perhaps to follow one smoothly moving target in a field of moving and stationary potential targets.

The cerebral cortex does not function in isolation. Cortical function is closely linked to the functions of the thalamus, basal ganglia, cerebellum, and numerous other subcortical structures. Furthermore, it is often not easy to discriminate between neural functions that are primarily sensory in nature and those that are predominantly motor. Often a cortical region seems to combine both sensory and motor properties. Even in primary somatomotor cortex (Brodman’s area 4), many neurons have discrete somatosensory receptive fields (Rosen and Asanuma, 1972; Lemon and

*Corresponding author. Tel.: +1 601 984 1657; Fax: +1 601 984 1655; E-mail: jclynh@anatomy.umsmed.edu

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Patricia Goldman-Rakic addressed this logical dilemma in a landmark theoretical paper in 1988:

“If subdivisions of limbic, motor, sensory, and associative cortex exist in developmentally linked and functionally unified networks, as the anatomical, physiological, and behavioral evidence reviewed here suggests, it may in the future be more useful to study the cortex in terms of information processing functions and systems rather than traditional but artificially segregated sensory, motor, or limbic components and individual neurons within only one of those components. Furthermore, in light of the detailed knowledge about specific interconnections at the cortical level, it is to be expected that more and more of this information will be used to guide physiological analysis of higher cortical function” (Goldman-Rakic, 1988).

Recent developments in the study of the cortical control of oculomotor behavior have brought us to the point where it is indeed “more useful to study the cortex in terms of information processing functions and systems rather than traditional but artificially segregated sensory, motor, or limbic components.” In this review, we will emphasize the functional interaction and anatomical interconnections of several distinct, well-delineated cortical regions that are particularly closely related to the control of voluntary gaze shifts. However, these regions will be discussed in their role as nodes in a distributed neural network in the cerebral cortex, rather than as “motor” or “sensory” components of the oculomotor system. For simplicity of discussion, we shall use the term “eye field” to refer to each of these regions, although, in addition to their shared properties related to the control of eye movements, each region also participates in other functions including higher cognitive functions such as memory, decision-making, remapping of sensory signals, modulation of attention, and planning of actions (see, e.g., Lynch, 1980; Sommer and Wurtz, 2000, 2001; Tanaka and Lisberger, 2001; Coe et al., 2002; Ferraina et al., 2002; Pierrot-Deseilligny et al., 2003). It should be noted in particular that neural activity related to the initiation of an eye movement can often be confused with neural activity related to shifts of visual attention, and that many experimental paradigms have been developed to attempt to discriminate between neural activity related to these two functions (see, e.g., Bushnell et al., 1981; Andersen et al., 1987, 1990b; Gnaadt and Andersen, 1988; Barash et al., 1991a, b; Snyder et al., 1997; Murthy et al., 2001; Andersen and Buneo, 2002; Goldberg et al., 2002; Bisley and Goldberg, 2003; Kusanoki and Goldberg, 2003).

The cortical regions that will be discussed in depth in this chapter include the frontal eye field (FEF), the parietal eye field (PEF), the supplementary eye field (SEF), the medial superior temporal area (MST), the prefrontal eye field region (PFEF) (also frequently referred to in the oculomotor literature as the dorsolateral prefrontal cortex, DLPFC), and a region on the medial surface of the parietal lobe that is called the precuneus region in human imaging studies and area 7m in monkey studies (Fig. 1). Each of these areas subserves multiple neural functions. The evidence that one of the functions of each of these regions is to

![Fig. 1. Approximate locations of six cortical eye fields in the macaque monkey brain. Area 7m is located on the medial surface of the hemisphere; the FEF, MST, PEF, and PFEF are located largely or entirely in the depths of the respective sulci. FEF, frontal eye field; MST, medial superior temporal area; PEF, parietal eye field; PFEF, prefrontal eye field; SEF, supplementary eye field.](image-url)
participate in the control of eye movements is as follows: (1) in each of these regions electrical stimulation will evoke eye movements; (2) in each of these regions neural activity is correlated with eye movements as demonstrated in single-neuron recording studies and functional imaging studies; (3) cortical damage or inactivation in each of these regions will impair eye movements; (4) each of these regions is strongly interconnected with other cortical areas concerned with eye movement control (as well as with other cortical areas not directly concerned with eye movements); and (5) each of these regions has direct connections to the brainstem oculomotor system. There are other regions that have been implicated in the control of eye movements by one or more of these criteria but which will not be discussed in detail here because they have not yet been studied in the same depth as those listed above. These include, for example, the postarcuate premotor cortex (Fadiga et al., 2000) and the anterior and posterior cingulate cortices (Berman et al., 1999).

Several major developments have contributed to the increased understanding of the role of the cerebral cortex in oculomotor control in the past 10–15 years. These include: (1) the discovery that the FEF includes a subregion devoted to the control of visual pursuit eye movements, as well as subsequent observations that indicate other eye fields also include both saccadic and pursuit subregions; (2) the steadily growing sophistication of behavioral neurophysiology experiments, particularly in the areas of antidromic identification of single neuron target structures and of reversible inactivation of cortical and subcortical oculomotor structures; (3) a steadily growing trend toward precise physiological identification of functional regions prior to the placement of neuroanatomical tracing agents; (4) the development of methods that permit the tracing of neural pathways across synapses, and thus allow the identification of second- and third-order neurons that project to a region or that receive projections from a region; (5) functional imaging experiments in humans, which have permitted the localization and functional definition of eye fields in awake humans; and (6) a large and growing body of evidence that now suggests the basic organization plan for the various cortical oculomotor areas is one of a distributed network rather than a primarily serial or hierarchical plan. All of these advances have had important influences on the understanding and appreciation of the neural connectivity of the oculomotor system. Conversely, our growing understanding of the neural connectivity has stimulated new approaches to some of the functional lines of research and has contributed significantly to the understanding of many of the results.

The present chapter will provide a brief review of the evidence for an oculomotor role for each of these cortical regions and then will concentrate on the neural connections of these regions. The connections of each eye field with subcortical structures will be described first, and then the cortico-cortical connections of the eye fields with one another will be described.

**Functional characteristics of eye fields**

Among the earliest experiments in which the generation of eye movements in primates could be unequivocally associated with one or another specific region of the cerebral cortex, the work of David Ferrier stands out. In 1875, Ferrier published the results of a series of experiments in which he exposed large areas of the cortex of anesthetized monkeys and described the various movements that were produced when the rudimentary electrical stimulation of the time was applied at different locations in the cortex (Ferrier, 1875, 1886). Stimulation at many loci produced movements of the contralateral limbs (Fig. 2). However, there were numerous sites where stimulation produced contraversive eye movements. These were located in the parietal lobe (labeled “13” and “13”’ in Fig. 2), the temporal lobe (labeled “14” in Fig. 2), and the frontal lobe (labeled “12” in Fig. 2). Ferrier’s observations were later confirmed and extended by others in monkeys (Beevor and Horsley, 1888) and apes (Beevor and Horsley, 1890; Grunbaum and Sherrington, 1903; Leyton and Sherrington, 1917) (for review, see Smith, 1944).

During the first part of the 20th century, investigators concentrated on the study of the region of
**Frontal eye field**

Although Ferrier’s original reports noted that eye movements were produced by stimulation of parietal and temporal cortices in addition to the frontal cortex, for the next 100 years the overwhelming majority of studies of motor activity concentrated on the frontal cortex. Perhaps the most influential of the early reviews in this regard is that by Smith in *The Precentral Motor Cortex* (1944, P.C. Bucy, editor), which reinforced the idea that motor activity was restricted to cortex anterior to the central sulcus and sensory activity resided in the cortex posterior to the central sulcus.

Most studies during the early half of the 20th century added only technical sophistication and additional species to Ferrier’s original experiments in anesthetized animals. A major advance was made by Wagman and colleagues (Wagman et al., 1958, 1961; Wagman, 1964) who used a *cerveau isolé* preparation that allowed stimulation of the cortex in unanesthetized monkeys. This preparation permitted eye movements of more nearly normal velocity to be evoked by electrical stimulation than was possible with anesthetized preparations. Robinson and Fuchs (1969) made another important advance by developing techniques that allowed the electrical stimulation of the cortex in awake, behaviorally trained monkeys. They demonstrated that the amplitude and velocity of electrically evoked eye movements obeyed the same main sequence relationship that naturally occurring saccadic eye movements did. Finally, Bruce et al. (1985) used microelectrodes for electrical stimulation. This greatly reduced the volume of tissue affected and permitted more precise localization of physiological functions.

The activity of single neurons in the region of the FEF has been studied in alert, trained monkeys, beginning in the late 1960s. Early experiments found activity related to visual stimuli (Mohler et al., 1973), and to direction of gaze, visually evoked saccades, and nystagmus fast phases (Birz, 1967, 1968; Birz and Schiller, 1970). However, in these early experiments, only neurons that had activity after the initiation of saccades were observed, primarily because recording sites were concentrated in relatively superficial

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Fig. 2. Ferrier’s original (1875) map of limb and eye movements evoked by electrical stimulation in the left hemisphere of a monkey. Ferrier’s original legend is as follows: “The left hemisphere of the monkey. 1. The opposite hind limb is advanced as in walking; 2, flexion with outward rotation of the thigh, rotation inwards of the leg, with flexion of the toes; 3, the tail; 4, the opposite arm is adducted, extended, and retracted, the hand pronated; 5, extension forwards of the opposite arm; a, b, c, d, movements of the fingers and wrist; 6, flexion and supination of the forearm; 7, retraction and elevation of the angle of the mouth; 8, elevation of the ala of the nose and upper lip; 9 and 10, opening of the mouth, with protrusion (9) and retraction (10) of the tongue; 11, retraction of the angle of the mouth; 12, the eyes open widely, the pupils dilate, and head and eyes turn to the opposite side; 13 and 13', the eyes move to the opposite side; 14, pricking of the opposite ear, head and eyes turn to the opposite side, pupils dilate widely.” (From Ferrier, 1875.)
cortex just anterior to the arcuate sulcus (Bizzi and Schiller, 1970). In 1981, Goldberg and Bushnell recorded from neurons deep in the anterior bank of the arcuate sulcus and found neurons that were active prior to the initiation of visually guided saccades (Goldberg and Bushnell, 1981). Bruce and Goldberg subsequently mapped a region of the anterior bank of the arcuate sulcus in macaque monkeys within which they were able to electrically evoke saccades at stimulus currents less than 50 μA (Bruce et al., 1985). This 50-μA stimulus threshold criterion has become a generally accepted, albeit somewhat arbitrary, criterion for measuring the location and extent of the FEF. Many neurons in this “low-threshold” FEF have activity that precedes the initiation of saccadic eye movements, other neurons have visual receptive fields, some have a combination of both movement and visual activity, and yet others have sustained, memory-related activity (Sommer and Wurtz, 2000, 2001). (For recent reviews, see Schall, 1997; Tehovnik et al., 2000.) The activity of some neurons in the FEF is modulated by vestibular input (Fukushima et al., 1999, 2000, 2001, 2004b) and some FEF neurons are active during convergence (Kurkin et al., 2003). Some neural activity in the FEF is associated with performance on an antisaccade task (when a saccade toward a visual target must be inhibited), but most current evidence suggests that the PF EF is more directly concerned with the inhibition of unwanted saccades than is the FEF (Pierrot-Deseiligny et al., 2003) (see also section “Prefrontal eye field”).

The modulation of visual attention is an important function of the FEF and has been described in single neuron recording studies and microstimulation studies in nonhuman primates and in functional imaging studies and transcranial magnetic stimulation studies in humans. Damage in the FEF induces attention disorders in both monkeys and humans, and is discussed below. Neural activity in the FEF is influenced by shifts in visual attention and target selection (Kodaka et al., 1997; Bichot et al., 2001; Schall, 2004; Thompson and Bichot, 2005; Thompson et al., 2005). Microstimulation in the FEF of nonhuman primates can produce shifts of visual attention (Moore and Fallah, 2001; Moore and Armstrong, 2003; Moore and Fallah, 2004). FEFs show increased activation in functional magnetic resonance imaging (fMRI) studies of visual attention and target selection (Corbetta, 1998; Corbetta et al., 1998, 2002; Corbetta and Shulman, 1998; Donner et al., 2000; Leonards et al., 2000; Gitelman et al., 2002). Finally, transcranial magnetic stimulation (TMS) over the FEF of humans has been shown, under certain conditions, to enhance visual attention (Grosbras and Paus, 2002).

Paradoxically, when the FEF is damaged or destroyed, the resulting impairment of saccadic eye movements is relatively mild and short-lasting. Bilateral lesions of the FEF in monkeys produce transient deficits of accuracy and latency that recover to a large extent within a few days or at most 1 or 2 weeks (Schiller et al., 1979, 1980; Deng et al., 1986; Lynch, 1992). Figure 3 illustrates typical saccade performance before and after bilateral FEF lesions by one of the monkeys reported by Lynch (1992).

Only modest impairment of saccades has been reported in humans following bilateral FEF

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**Fig. 3.** Saccadic eye movements before and after bilateral destruction of the FEF. Fourteen eye position traces are superimposed in each grouping. Dashed line indicates the time at which the fixation target jumped from the center of the monkey’s visual field to 24° to the left. Note that there is little difference in accuracy and latency between visually guided saccades before and after a large bilateral lesion of the FEF. (Unpublished data from the study reported in Lynch, 1992.)
damage (Pierrot-Deseilligny, 1994; Rivaud et al., 1994; Pierrot-Deseilligny et al., 2002). In contrast, damage to posterior parietal cortex produces increased latencies into the contralateral visual field in both monkeys (Lynch and McLaren, 1989) and humans (Pierrot-Deseilligny et al., 1991; Braun et al., 1992).

FEF damage does produce a major impairment of saccades to remembered targets in both monkeys (Deng et al., 1986) and humans (Pierrot-Deseilligny et al., 1991, 2002). In addition, cortical damage that includes the FEF produces visual perception deficits (Latto, 1977), whereas subthreshold electrical stimulation in the FEF enhances visual discriminations (Tirin and Fallah, 2004). Finally, FEF is well known to produce a profound contralateral neglect in monkeys (Ferrier and Yeo, 1884; Kennard and Ectors, 1938; Latto and Cowey, 1971) and related symptoms in humans (Foerster, 1936; Holmes, 1938; Mettler, 1949; Heilman and Valenstein, 1972). However, the symptoms typically resolve within a few days to a few weeks.

The specific contribution of the FEF to eye movement control has more recently been investigated using reversible chemical inactivation of the FEF in monkeys as they are performing learned oculomotor tasks (Sommer and Tehovnik, 1997; Dias and Segraves, 1999). Cortical inactivation produced while a monkey is performing an oculomotor task produces generally more serious deficits than those that are observed after surgical lesions. However, monkeys typically will not perform oculomotor tasks for 3 or 4 days following a large lesion of the FEF due to the profound contralateral neglect that also follows the lesion. Both the neglect and the oculomotor deficit resolve at about the time the monkey is capable of performing the behavioral task, presumably because other elements in the oculomotor system are able to quickly take over some of the functions that are normally performed by the FEF. The duration of the deficits produced by reversible inactivation have not yet been reported, and the interaction between the visual neglect and the purely oculomotor performance has not yet been carefully studied. The dramatic effect of FEF inactivation upon oculomotor control may be to some extent analogous to the effect on an individual’s balance that is produced by the loss of vestibular function from trauma, stroke, or antibiotic poisoning. At first, the individual experiences vertigo and loss of balance, and is severely impaired in walking, manipulation of objects, and even reading. With time, however, the visual and somatosensory systems compensate to a large extent and the individual is again able to function reasonably well in many situations (for example, see J.C., 1952).

One of the major changes in recent years in the understanding of the cortical control of eye movements is the recognition that each of the cortical eye fields is concerned with both saccadic and visual pursuit eye movements. Lynch (1987) reported that bilateral destruction of the FEF in monkeys produced an inability to produce a smooth tracking movement that matched the speed of the visual target (Fig. 4A). The monkey was able to follow the target only with a series of catch-up saccades interposed between brief periods of too-slow smooth eye movements. The involvement of the FEF in visual pursuit was soon confirmed in other laboratories (MacAvoy et al., 1991; Keating, 1991). Bruce and colleagues demonstrated that microstimulation in the fundus of the arcuate sulcus could evoke slow, smooth eye movements (Gottlieb et al., 1993) and that neurons in that region had activity closely related to visual pursuit eye movements (Gottlieb et al., 1994). Reversible inactivation of the FEFsem impairs smooth pursuit eye movements (Shi et al., 1998). The contribution of the FEFsem to oculomotor control has been extensively investigated in recent years (Tanaka and Fukushima, 1998; Fukushima et al., 1999, 2000, 2004b; Tanaka and Lisberger, 2001, 2002a, b, c). The physical relationship between the pursuit subregion (FEFsem) and the saccade subregion (FEF sac) in macaque monkeys is shown in Fig. 4B.

**Parietal eye field**

The PEF, located in the lateral bank of the intraparietal sulcus (LIP), fulfills each of the above-listed criteria for an eye field. The function of posterior parietal cortex in the initiation and
control of voluntary eye movements was not studied intensively until the behavioral neurophysiology studies of Mountcastle and his colleagues in the early 1970s (Mountcastle et al., 1975; Lynch et al., 1977). These studies were the first to report neural activity in the cerebral cortex that preceded the initiation of an eye movement. Presaccadic activity in the lateral bank of the intraparietal sulcus (designated LIP by Andersen) (Andersen et al., 1985) has subsequently been reported in numerous studies (Andersen et al., 1987, 1990b; Barash et al., 1991a, b). Parietal activity precedes saccades made to the remembered location of a visual target that has been extinguished well before the eye movement was made (Andersen et al., 1987; Gnadt and Andersen, 1988; Barash et al.,
Some neurons in LIP have activity that precedes saccades made to the location of an acoustical signal in total darkness (Mazzoni et al., 1996).

Electrical stimulation in parietal cortex, both within LIP and in surrounding regions, can evoke saccadic eye movements (Ferrier, 1975; Fleming and Crosby, 1955; Wagman, 1964; Shibutani et al., 1984; Keating and Gooley, 1988; Kurylo, 1991; Kurylo and Skavenski, 1991; Thier and Andersen, 1996). Electrical-stimulus-evoked eye movements occur even after bilateral ablation of the FEF (Keating et al., 1983), and parietal stimulation can modify the trajectory of visually guided saccades (Mushiake et al., 1999).

Oculomotor impairment following damage to the PEF alone is modest, including small increases in the latency of saccadic and pursuit eye movements in monkeys and humans (Lynch, 1980; Lynch and McLaren, 1982; Pierrot-Deseilligny et al., 1987; Lynch and McLaren, 1989; Braun et al., 1992; Heide and Kompf, 1998; Wauschkuhn et al., 1998). Decrease of saccade accuracy has also been observed in humans following lesions in the pathway from the PEF to the superior colliculus (Gaymard et al., 2003). In addition, a significant impairment of visual attention in the contralateral visual field occurs (Lynch and McLaren, 1989), although not as strong as the contralateral neglect that is produced by parietal lobe damage in humans. As in the case of the FEF, the rapid recovery of function during the surgical recovery period may be a factor in the small magnitude of the oculomotor deficit. The oculomotor impairment produced by chemical inactivation of LIP while a monkey is performing a behavioral task is considerably greater than that observed after recovery from a surgical lesion (Li et al., 1999; Li and Andersen, 2001).

If a surgical lesion of the PEF is combined with a surgical lesion of the FEF, the resulting oculomotor impairment is much more profound and long-lasting than that produced by either lesion alone (Fig. 5) (Lynch, 1992). This observation suggests that there is a certain amount of redundancy in the oculomotor function of the FEF and PEF, and that the loss of one eye field is to some extent compensated by the presence of the other. The possibility that the PEF participates in a distributed network of regions devoted to oculomotor control has been proposed (Lynch, 1980; Tian and Lynch, 1996b) and will be discussed below.

Neural activity in LIP and 7a was also observed to be associated with visual pursuit movements in the original experiments of Mountcastle (Mountcastle et al., 1975; Lynch et al., 1977) and subsequently by other investigators (Sakata et al., 1983;
Kawano et al., 1984; Bremmer et al., 1997a). Electrical microstimulation of parietal cortex has produced slow, smooth eye movements (Kurlyo and Skavenski, 1991). Lesions of parietal cortex produce mild deficits of visual pursuit eye movements (Lynch and McLaren, 1982). Combined lesions of the PEF and the FEF produce greater pursuit impairment than do lesions restricted to either the PEF or the FEF (Lynch, unpublished observations). fMRI has confirmed that parietal cortex in humans has increased activity during visual pursuit tasks (Petit et al., 1997; Luna et al., 1998; Petit and Haxby, 1999).

Supplementary eye field

The SEF was first described by Schlag and Schlag-Rey (1985, 1987a) as a region in the dorsomedial frontal cortex in which neurons discharged before saccadic eye movements. The neural activity in the SEF has been studied extensively (Mann et al., 1988; Mitz and Godschalck, 1989; Schall, 1991; Russo and Bruce, 1993, 1996; Tehovnik and Lee, 1993; for reviews, see Schall, 1997; Tehovnik et al., 2000). Microstimulation within the SEF evokes saccadic eye movements (Schlag and Schlag-Rey, 1987a, b; Tehovnik and Lee, 1993; Lee and Tehovnik, 1995; Russo and Bruce, 1996).

In addition to its role in saccadic eye movements, recent behavioral neurophysiology studies in monkeys and fMRI studies in humans have demonstrated that the SEF is also involved in pursuit eye movements. Microstimulation in the SEF can induce slow, smooth eye movements (Tian and Lynch, 1995) or can facilitate ongoing visual pursuit (Missal and Heinen, 2001). Some neurons in the SEF have activity that is modulated during visual pursuit (Heinen, 1995; Heinen and Liu, 1997; Fukushima et al., 2004a). The SEF region in humans shows increased activation during fMRI studies of visual pursuit in humans (Luna et al., 1998; Petit and Haxby, 1999).

Lesion studies in monkeys have reported only very mild oculomotor impairment after reversible inactivation of the SEF (Schiller and Chou, 1998; Sommer and Tehovnik, 1999).

Medial superior temporal area

The MST is a visuomotor area located in the medial portion of the posterior upper bank of the superior temporal sulcus in macaque monkeys (Maunsell and van Essen, 1983; Desimone and Ungerleider, 1986; Boussaoud et al., 1990). Many neurons in MST are active during pursuit eye movements (Dursteler and Wurtz, 1988; Komatsu and Wurtz, 1988; Newsome et al., 1988; Ferrera and Lisberger, 1997; Bremmer et al., 1997b), including anticipatory pursuit movements and pursuit of imagined targets (Ilg, 2003; Ilg and Thier, 2003). Neural activity related to convergence eye movements has also been reported in MST (Inoue et al., 1998; Takemura et al., 2001; Akao et al., 2005). Most neurons in MST are responsive to stimulus disparity (Roy et al., 1992). Electrical stimulation in MST modulates ongoing visual pursuit eye movements (Komatsu and Wurtz, 1989); and inactivation of MST produces an ipsilateral pursuit deficit (Dursteler and Wurtz, 1988). A region in the presumed location of MST in humans is activated in fMRI studies of visual pursuit (de Oliveira et al., 1997). Neural activity related to saccadic eye movements has not yet been reported in MST, although the region does project to the saccadic subregion of the FEF (Tian and Lynch, 1996b).

Prefrontal eye field

The PFEF (which occupies a portion of the DLPFC) is densely interconnected with the FEF and also contributes to the control of voluntary eye movements, but its influence appears to be primarily inhibitory — to suppress unwanted saccades rather than to initiate wanted saccades. Humans with damage in the PFEF have particular difficulty in suppressing saccades to a visual target in an antisaccade task (where the instruction is to make a saccade away from a visual target when it appears in the visual field) (Guitton et al., 1985; Pierrot-Deseilligny et al., 1991). The role of the PFEF in the antisaccade paradigm has also been demonstrated in PET, fMRI, and TMS studies.
(Sweeney et al., 1996; Muri et al., 1998) (for review, see Pierrot-Deseilligny et al., 2003, 2004).

Although the suppression of unwanted saccades appears to be a major function of the PFEF, it also plays a role in the generation and control of visually guided and memory guided saccades. Directionally selective presaccadic neural activity has been observed in the PFEF (Funahashi et al., 1991), as well as activity related to the spatial location of stimuli that serve as saccade targets (Funahashi et al., 1990; Takeda and Funahashi, 2002). Neural signals in the PFEF code parameters of memory-guided saccades (Funahashi et al., 1993b) and lesions of the PFEF produce impairment of the accuracy of memory-guided saccades (Funahashi et al., 1993a).

Precuneus (PCun or 7m)

Area 7m, on the medial wall of the hemisphere, has not been studied physiologically as extensively as the other eye fields discussed here. However, recent studies have reported that microstimulation in parietal cortex in the medial wall of the hemisphere can evoke saccadic eye movements (Thier and Andersen, 1998) and that many neurons in that region carry combined gaze direction and hand reaching signals (Ferraina et al., 1997a, b). The precuneus region (considered to be the human equivalent of area 7m) shows enhanced activity during oculomotor tasks in fMRI experiments (Petit and Haxby, 1999). Area 7m is connected with other oculomotor regions in the cortex (Cavada and Goldman-Rakic, 1989a, b; Tian and Lynch, 1996b; Leichnetz, 2001) and with subcortical oculomotor structures (Leichnetz, 2001). All of this evidence supports the idea of an oculomotor role for the precuneus region.

Evidence from functional imaging experiments

The advent of fMRI and positron emission tomography (PET) has made it possible to visualize areas of increased neural activity in the brains of conscious humans while they perform sensory, motor, and intellectual tasks. These techniques have been particularly advantageous in the study of the oculomotor system because eye movements can be effectively quantified using simple visual stimuli that can be conveniently viewed by subjects inside the large and cumbersome scanners and because eye movements are so small that movement artifacts in the imaging processes are minimized. The use of fMRI and PET in the study of the oculomotor system is discussed in detail in Chapter 16. Here, we shall only mention a few studies that directly support our classification of eye movement related regions of the cerebral cortex. Early PET studies demonstrated increased activity during visually guided saccade tasks in the FEF, SEF, and PEF (Anderson et al., 1994; Sweeney et al., 1996). The increased resolution that is possible in the fMRI allowed the location of the FEF, SEF, and PEF in humans to be defined more precisely (Muri et al., 1996; Petit et al., 1997; Luna et al., 1998; Petit and Haxby, 1999). Eye movement related activity in the parietal lobe was observed in the banks of the intraparietal sulcus, in a region analogous to LIP in monkeys, and also in the precuneus, a region in the parietal lobe on the medial surface of the hemisphere (Luna et al., 1998). The fMRI technique also demonstrated

Fig. 6. Increased cortical activity during a visual pursuit task (red outline) and a saccade task (yellow outline) superimposed onto the subject’s Talairach-normalized axial structural image. The axial plane illustrated is +46 mm above the bicommissural plane (through the anterior and posterior commissures). The FEF, PEF, SEF, and precuneus are visible in this slice; activity in the MST region is shown in a more inferior slice in the original illustration. (Adapted from Fig. 3 of Petit and Haxby, 1999.)
adjacent but separate regions in the FEF of humans, one of which is active during visual saccade tasks and the other during visual pursuit tasks (Petit et al., 1997; Petit and Haxby, 1999; Rosano et al., 2002). Finally, recent fMRI studies have shown that the FEF, SEF, PEF, MT/MST region, and the precuneus each have increased activity during oculomotor tasks, as shown in Fig. 6, and that in each region the portion that is activated during a saccade task is separate from but adjacent to (or partially overlapping with) the portion that is activated during a visual pursuit task (Berman et al., 1999; Petit and Haxby, 1999). Thus, the organization of the cortical oculomotor system in humans is remarkably similar to the cortical organization demonstrated in monkeys by Tian and Lynch (1996b).

Cytoarchitecture

The cytoarchitectural organization of the cortical eye fields ranges from classical homotypical association cortex with six clearly distinct layers, typified by the PEF and MST, to cortex that is essentially agranular premotor cortex, including the SEF and the pursuit region of the FEF. At the homotypical end of the continuum of cytoarchitectural types, the PEF occupies a portion of the inferior parietal lobe in monkeys and humans that Brodmann originally classified as area 7 (Brodmann, 1925) and which was classified as area PG by von Bonin and Bailey (1947). More recently, the cortex of the inferior parietal lobule has been divided into as many as eight distinct subregions (see discussions in Cavada and Goldman-Rakic, 1989a; Preuss and Goldman-Rakic, 1991a). The lateral wall of the intraparietal sulcus (area LIP) has been classified as area POa (Seltzer and Pandya, 1980; Pandya and Seltzer, 1982) or area 7ip (Cavada and Goldman-Rakic, 1989a). However, all of the subregions, together with nearby area MST and the precuneus (or 7m) on the medial wall of the hemisphere, share the basic characteristics of six well-defined layers, including in particular a substantial internal granular layer (IV).

One criterion for the cytoarchitectural classification of a region of cerebral cortex as “motor,” “sensory,” or “association” is the degree of development of layer IV, the internal granular layer, which is the primary receiving zone for thalamocortical afferents originating in the relay nuclei of the thalamus. Primary receiving areas have thick, well-developed internal granular layers and are termed “granular” cortex; motor areas such as Brodmann’s areas 4 and 6 have only very faint internal granular layers and are termed “agranular” cortex; association cortex regions have well-defined internal granular layers that are not as thick nor as complex as those in primary sensory areas. Association areas are classified as “homotypical” or “eulaminate” cortex.

At the agranular end of the continuum of cytoarchitectural organization of cortical eye fields, the SEF is located in a subdivision of Brodmann’s area 6 that has been designated 6αβ (Vogt and Vogt, 1919), 6DR (Barbas and Pandya, 1987), or F7 (Matelli et al., 1991); see also Tian and Lynch (1996b). This cortex is very similar to the agranular premotor cortex. The internal granular layer is absent or very thin and faint, with layers III and V often merging together and with layer VI thicker than in prefrontal homotypical cortex.

The pursuit subregion of the FEF is located in the fundus and posterior bank of the arcuate sulcus in macaque monkeys (see Fig. 5) and on the medial shoulder of the posterior bank of the superior arcuate sulcus in Cebus monkeys (Tian and Lynch, 1996a). This functional region, like the SEF, is also located in transitional, almost agranular cortex (6αβ or 6DR) (Cebus monkeys: Tian and Lynch, 1996a; macaque monkeys: Stanton et al., 1989).

The cytoarchitectural organization of the FEF sac lies between the two extremes described above. The functionally defined saccade subregion of the FEF extends into two distinct cytoarchitectural fields, Walker’s areas 8A and 45 (Walker, 1940; Stanton et al., 1989). The cytoarchitectural organization of the FEF sac is more similar to that of the PEF than to the SEF. The majority of the cortex in the anterior bank of the arcuate sulcus in macaque monkeys (and in the entire anterior bank in Cebus monkeys) has six well-defined layers, with a robust internal granular layer and numerous medium-to-large pyramidal cells in layer V (von Bonin,
1938; Walker, 1940; Stanton et al., 1989; Preuss and Goldman-Rakic, 1991b; Tian and Lynch, 1996a). This granular cortex occupies the upper one-half to two-thirds of the anterior bank of the arcuate sulcus in macaque monkeys (Walker, 1940, p. 65), where Sommer and Wurtz have carefully mapped the area in which neurons that project to the intermediate layers of the superior colliculus are located (Sommer and Wurtz, 2000). In the lower part of the anterior bank, the internal granular layer gradually disappears and the cytoarchitecture transitions to the 6aβ cytoarchitecture of the FEFsem (Fig. 5) and then to the 6az (6DC) cortex that characterizes the premotor cortex of the upper part of the posterior bank of the arcuate sulcus (Barbas and Pandya, 1987; Stanton et al., 1989; Tian and Lynch, 1996a).

The FEF in humans, localized using fMRI, is in the anterior bank of the precentral sulcus at about the level of the intersection with the superior frontal sulcus. It has a distinct internal granular layer and is therefore not within Brodmann’s area 6 proper as previously supposed, but rather is predominantly just anterior to area 6, in a transition region between area 6 and area 8 and extending into area 8 proper (Rosano et al., 2003).

**Subcortical connections of eye fields**

Each of the six eye fields described above has direct projections to one or more subcortical structures that are important for oculomotor control (Fig. 7). These structures include the superior colliculus, the pontine nuclei (and thence to the cerebellum), the mesencephalic and pontine reticular formations (PRFs), a number of thalamic nuclei, the caudate and putamen, and others. We will discuss the subcortical connections of each eye field in turn, concentrating on the efferent connections. The afferent input from subcortical structures will be discussed in greater detail in the section on the thalamus. As much as possible, we shall concentrate on anatomical studies in which the critical functional regions have been defined physiologically or in which it is possible to compare directly the boundaries of injected regions with other, comparable studies in which the respective regions were physiologically identified. Because of space limitations, we will concentrate on the ipsilateral connections of the eye fields, although there are sometimes small but definite contralateral counterparts to the ipsilateral subcortical connections and significant cortico-cortical connections with the respective eye fields in the opposite hemisphere.

**Frontal eye field**

The FEF occupies portions of areas 8a and 45 of Walker (Walker, 1940), located in the anterior bank of the arcuate sulcus in macaque and cebus monkeys and in the lateral frontal cortex of squirrel and owl monkeys. Many studies of the subcortical projections of this general region were conducted before physiological localization became routine (e.g., Kuypers and Lawrence, 1967; Astruc, 1971; Kunzle and Akert, 1977; Leichnetz, 1980; Leichnetz et al., 1981, 1984a, b; for review of earlier work, see Huerta et al., 1986). However, in the early studies there was always a question as to whether the tracer placements were restricted only to the functional FEFs or if they also involved adjacent, nonoculomotor cortex.
Huerta et al. (1986) were the first to carefully map out the region of cortex within which microstimulation at currents of less than 50 μA evoked saccadic eye movements; mark the boundaries of the excitable region with electrolytic lesions that were visible in histological sections; and then restrict the tracer placement to the electrically excitable region of cortex. They used this technique to map the efferent projections from the saccade subregion of the FEF (FEFsac) to the thalamus and brainstem in macaque monkeys, squirrel monkeys, and owl monkeys. Their tracer (horseradish peroxidase conjugated to wheat germ agglutinin) revealed both the sources of afferent input to the FEF and the targets of efferent output of the FEF. This study stands out both for the great technical care with which the tracers were placed in functionally identified regions of the cortex and also for the quality of the figures, which illustrate clearly the relative density of the observed labeling in the various diencephalic and brainstem structures.

Figure 8 shows the functionally identified injection site in case MM-85-68 from Huerta et al. (1986). Figure 9 illustrates the primary results from this injection. Efferent targets containing labeled axons and axon terminals are indicated by thin lines; labeled cell bodies of neurons that project to the FEF are indicated by small dots. The strongest labeling was found in the superior colliculus, the pontine nuclei, and the thalamus.

The superior colliculus had a dense zone of labeled terminals in the intermediate and deep layers, with the strongest labeling concentrated in a series of patches in the stratum griseum intermediate. This pattern is significant because the intermediate layers of the colliculus are the site of neurons which discharge immediately before saccadic eye movements (Mohler and Wurtz, 1976; Mays and Sparks, 1980; Hikosaka and Wurtz, 1983; Ma et al., 1991) and which project directly to premotor regions in the brainstem oculomotor system (Harting, 1977; May and Porter, 1992). The axons from the FEFsac terminated in a series of dense patches separated by unlabeled zones. The patches of labeled terminals coincide with zones of high concentrations of acetylcholinesterase, and also coincide with patches of label arising from injections in the substantia nigra, pars reticulata (another region in which eye-movement-related neural activity is present) (Illing and Graybiel, 1985).

In the thalamus, Huerta et al. (1986) observed dense reciprocal connections with the ipsilateral pars multiformis portion of the mediodorsal nucleus (MDmfl) and the medial portion of the ventral anterior nucleus (VA) (particularly the pars multiformis). Retrograde and anterograde labeling was also observed in the paracentral, central lateral, and parafascicular nuclei, nucleus limitans,
Fig. 9. Afferent and efferent connections of the saccade-related FEF with the thalamus and brainstem in macaque monkey. The primary axonal targets of the FEF include the multiform (or paralaminar) portion of the mediodorsal nucleus (MDmf); layer IV (stratum griseum intermedium) of the superior colliculus (IV); and the pontine gray (PG), which relays neural information to the cerebellum. For additional abbreviations, see “Abbreviations” list. (From Fig. 3 of Huerta et al., 1986.)
and in the medial pulvinar has been reported. Saccade-related neural activity has been reported in most of these nuclei, as well as the paralaminar portions of the ventral lateral (VL) and ventral posterolateral, pars oralis (VPLo) (Sommer and Wurtz, 2002, 2004a, b; Tanibuchi and Goldman-Rakic, 2003, 2005; Wyder et al., 2003, 2004; Watanabe and Funahashi, 2004a, b). The general pattern of labeling observed by Huerta has been confirmed in numerous laboratories (Goldman-Rakic and Porrino, 1985; Asanuma et al., 1985; Stanton et al., 1988a; Barbas et al., 1991; Tian and Lynch, 1997). Thalamic connections of the cortical eye fields will be discussed in greater detail later in the chapter.

The physiologically identified FEF projects to the medial, dorsolateral, and intermediate pontine nuclei on the ipsilateral side, and has bilateral projections to the nucleus reticularis tegmenti pontis (NRTP) (Huerta et al., 1986). These regions are well known to participate in oculomotor control (Suzuki and Keller, 1984; Crandall and Keller, 1985; May et al., 1988; Mustari et al., 1988; Thier et al., 1988; Suzuki et al., 1990, 1999, 2003; Scudder et al., 1996; Yamada et al., 1996; Van Opstal et al., 1996; Ono et al., 2005). The projections to the pontine nuclei were distributed in small, isolated patches within the various nuclei. The regions of labeling extended over most of the rostral-caudal extent of the pontine nuclei. This pattern of labeling was also reported by Stanton et al. (1988b), as well as earlier investigators who placed tracers in the FEF using anatomical landmarks (Kunzle and Akert, 1977; Leichnetz et al., 1984a; Leichnetz, 1989). (See also Chapter 10.)

The individual FEFsac and FEFsem were localized physiologically in Cebus monkeys by Yan et al. (2001b) and anterogradely transported tracers were placed in the two regions. Corticopontine projections from both the FEFsac and FEFsem were located predominantly in the dorsomedial and paramedian pontine nuclei, with considerable apparent overlap of the two distributions. The lack of labeled FEFsem terminals in the DLPN in Cebus monkeys is probably a species difference.

The FEF also projects to the zona incerta, rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), a zone just medial to the rostral portion of the red nucleus, the nucleus of Darkschewitsch (nD), the interstitial nucleus of Cajal (iC), the subthalamic nucleus, and the mesencephalic and pontine reticular formation (Huerta et al., 1986; Stanton et al., 1988b; Yan et al., 2001a).

The FEF projects heavily to the basal ganglia. Tracer injections in the physiologically identified FEFsac produce dense regions of terminal labeling in the body and head–body junction of the caudate and less dense patches of labeled terminals in the putamen (Graybiel and Ragsdale, 1979; Stanton et al., 1988a; Shook et al., 1991; Leichnetz and Gonzalo-Ruiz, 1996; Cui et al., 2003). The caudate nucleus contains neurons with activity that is time-locked to saccadic eye movements (Hikosaka et al., 1989, 2000); chemical lesions of the caudate produce disorders of saccadic eye movements (Kato et al., 1995; Kori et al., 1995); and stroke that affects the body of the caudate in humans produces saccade deficits (Vermersch et al., 1999). (See also Chapter 14.)

Recent studies suggest that the basal ganglia are also important in the control of pursuit eye movements. The physiologically identified FEFsem projects to the caudate and putamen, with terminal fields as dense and as large in area as the FEFsac terminal fields (Cui et al., 2003). Activation of the caudate has been observed during pursuit eye movement tasks in a PET study in humans (O’Driscoll et al., 2000).

Of the four primary projections from the FEF to brainstem oculomotor centers (SC, pontine nuclei, basal ganglia, and mesencephalic and PRF), the one that is the most controversial in its strength and function is that from the FEF to the PRF. This pathway may be responsible for the preservation of function that permits a monkey to recover quickly and make relatively normal saccades soon after the superior colliculus has been destroyed (Schiller et al., 1979, 1980, 1987; Albano et al., 1982). Saccades can still be evoked by electrical stimulation of the FEF after surgical destruction of the superior colliculus (Schiller, 1977; Schiller and Sandell, 1983), but not after acute inactivation of the SC (Hanes and Wurtz, 2001). Although a number of investigators have reported that there is a projection from the FEF to the PRF (Leichnetz et al., 1984a; Schnyder et al., 1985;
Huerta et al., 1986), the projection terminates diffusely, is weak and irregular in its density, and occasionally is not observed at all (see Stanton et al., 1988b). Further investigation is necessary to determine whether the FEF-to-PRF pathway is responsible for the rapid recovery of saccadic function following destruction of the superior colliculus, or if the FEF-to-pontine-nuclei-to-cerebellum is more important in this regard. (See also Chapter 5.)

For recent reviews of the physiology and anatomy of the FEF, see Leichnetz and Goldberg (1988), Schall (1997), and Tehovnik et al. (2000).

**Parietal eye field**

The subcortical projections of the PEF are primarily to the superior colliculus, pontine nuclei, and basal ganglia. In the superior colliculus, axons from LIP terminate predominantly in the stratum griseum intermediale and extend into stratum griseum profundum (Lynch et al., 1985). In contrast, the adjacent cortical area 7a, which is less directly implicated in the control of saccades than LIP, projects only sparsely to the SC. Thus, the parieto-tectal axon terminals overlap the terminals of projections from the FEF to a considerable extent, although the fronto-tectal terminals are most concentrated in the superficial half of the SGI, and extend into the stratum opticum (Lynch et al., 1985; Huerta et al., 1986). A return projection from the SC to LIP via the pulvinar has been demonstrated using the transneuronal transport of Herpes virus (Clower et al., 2001). This projection originates predominantly in the stratum opticum, more superficially than the zone containing the terminals of the parieto-tectal projection, but overlapping somewhat with the region of termination of the fronto-tectal projection.

The PEF projects to the dorsal and dorsolateral pontine nuclei, structures that participate in the control of pursuit eye movements (May and Andersen, 1986; Schmahmann and Pandya, 1989; Ono et al., 2005). The PEF also sends a moderate projection to the lateral pontine nuclei, which overlap with the projection from the adjacent area 7a on the convexity of the hemisphere.

The PEF sends an extensive projection to the caudate and putamen (Cavada and Goldman-Rakic, 1991; Baizer et al., 1993; Yeterian and Pandya, 1993). In the caudate, labeled terminals are most dense in the body, extending over a large portion of the region. Some labeled terminals were also observed in the dorsolateral portions of the head and the tail of the caudate (Cavada and Goldman-Rakic, 1991). Labeling in the putamen was less dense than in the caudate and concentrated medially over most of the antero-posterior extent of the putamen (Cavada and Goldman-Rakic, 1991; Baizer et al., 1993). The PEF also projects to the claustrum (Baizer et al., 1993).

Connections of the PEF with the thalamus are predominantly with the medial and lateral pulvinar (Asanuma et al., 1985; Schmahmann and Pandya, 1990; Baizer et al., 1993). The zones of terminal labeling of parieto-pulvinar axons are arranged in horizontal bands (Asanuma et al., 1985; Hardy and Lynch, 1992; Baizer et al., 1993), with bands of terminals in the medial pulvinar that originate in the LIP interdigitated between bands of terminals from 7a (Hardy and Lynch, 1992). The lateral pulvinar projects preferentially to LIP rather than 7a (Hardy and Lynch, 1992). The PEF also receives input from the dorsolateral and lateral posterior nuclei, the pars postrema of the ventral lateral nucleus, and the nucleus centralis superior lateralis (Schmahmann and Pandya, 1990).

**Supplementary eye field**

The subcortical connections of the SEF are similar to those of the FEF. Dense labeling of the intermediate and deep layers of the superior colliculus is observed after physiologically guided injections of the SEF (Huerta and Kaas, 1990; Shook et al., 1990). The SEF projects more densely to the deeper layers of the SC than does the FEF. The labeling is overwhelmingly ipsilateral (Huerta and Kaas, 1990; Shook et al., 1990), although a few contralateral terminals have been seen, particularly in layer I of the SC (stratum zonale) (Shook et al., 1990). The SEF projects to the dorsomedial, paramedial, and medial ventral pontine nuclei,
predominantly on the ipsilateral side, and bilaterally to the nucleus reticularis tegmenti pontis (Huerta and Kaas, 1990; Shook et al., 1990). The SEF, together with the FEF, projects to the PRF, although there are some differences between the two projections. Both the SEF and FEF project to the nucleus raphe interpositus (Schnyder et al., 1985; Huerta et al., 1986; Huerta and Kaas, 1990; Shook et al., 1990), a region in which omnipause neurons (which are critical for the triggering of saccades) are concentrated (Büttner-Ennever and Büttner, 1988). The projection is predominantly ipsilateral, but with a significant contralateral component. In contrast, the SEF but not the FEF projects to the medial nucleus reticularis pontis oralis (Shook et al., 1990), the region in which saccade burst neurons are concentrated (Hepp and Henn, 1983).

Medial superior temporal area

The MST projects heavily to the dorsolateral and dorsal pontine nuclei (Glickstein et al., 1980; Tusa and Ungerleider, 1988; Boussaoud et al., 1992; Distler et al., 2002), a region of the pontine nuclei known to participate in the control of pursuit eye movements. Lesser projections have been observed to the most caudal portion of the tail of the caudate nucleus and the caudal putamen, the claustrum, the pretectum, and the basal forebrain (Boussaoud et al., 1992; Distler and Hoffmann, 2001; Distler et al., 2002).

Prefrontal eye field

The PFEF, located in area 46 of the dorsolateral prefrontal cortex, projects densely to the intermediate and deep layers of the SC (Goldman and Nauta, 1976; Leichnetz et al., 1981; Fries, 1984) and to the head and body of the caudate nucleus (Goldman and Nauta, 1977; Graybiel and Ragsdale, 1979; Yeterian and Pandya, 1991). The PFEF also projects to the pontine nuclei (Schmahmann and Pandya, 1997a, b).

Thalamic input to area 46 arises predominantly from the dorsomedial nucleus (DMm) (Goldman- Rakic and Porrino, 1985; Giguere and Goldman-Rakic, 1988; Barbas et al., 1991; Middleton and Strick, 2001), the ventral anterior nucleus (VARc and VAnc) (Goldman-Rakic and Porrino, 1985; Barbas et al., 1991; Middleton and Strick, 2001), the anterior nuclear group (Goldman-Rakic and Porrino, 1985), and the medial pulvinar nucleus (Goldman-Rakic and Porrino, 1985; Barbas et al., 1991; Romanski et al., 1997). Transsynaptic transport experiments have demonstrated that area 46 participates in both cerebellar and basal ganglia feedback loop circuits (Middleton and Strick, 1994, 2000, 2001, 2002; Kelly and Strick, 2003, 2004) and that one of the regions of the cerebellum in which Purkinje cells are labeled after injections in area 46 is lobule VII of the vermis, a region known to be involved in oculomotor control (Leigh and Zee, 1999). (See also Chapter 8.)

Precuneus (area 7m)

The functional roles of the precuneus regions have only recently been associated with oculomotor control, and the anatomical connections of 7m have not yet been studied in as much detail as those of the other oculomotor regions discussed here. Nevertheless, it is known that 7m projects to the intermediate layers of the superior colliculus (Leichnetz, 2001), the pretectal region (Leichnetz, 2001), the dorsolateral head and body of the caudate nucleus and putamen (Yeterian and Pandya, 1993; Leichnetz, 2001), and the dorsolateral, dorsal, and lateral pontine nuclei and NRTP (Schmahmann and Pandya, 1989; Leichnetz, 2001). Additional projections have been described to the nucleus of Darkschewitsch, claustrum, zona incerta, and parvicellular red nucleus (Leichnetz, 2001).

The major thalamic connections of area 7m include the dorsal portion of the ventral lateral nucleus, pars caudalis (VLc) (approximately the same region that projects to the FEFsem), lateral posterior (LP), medial and lateral pulvinar nuclei, and the intralaminar nuclei CL and CSL (Yeterian and Pandya, 1985; Schmahmann and Pandya, 1990; Leichnetz, 2001).
Thalamic connections and feedback circuits

The thalamus is known to play an important role in the control of eye movements. Among the earliest reports of eye-movement-related activity in the thalamus are the studies of Schlag and Schlag-Rey, who reported neural activity in the central thalamic region, particularly in the intralaminar nuclei, which was related to spontaneous and voluntary eye movements (Schlag-Rey and Schlag, 1984; Schlag and Schlag-Rey, 1984). Over the succeeding two decades, few additional studies addressed the role of the intralaminar nuclei in eye movement control. Two recent single neuron recording studies have reported neural activity related to the sensory, delay, and motor aspects of saccade tasks in the “central thalamic region,” a region that includes several intralaminar nuclei but also paralaminar portions of the mediodorsal, ventral anterior, and ventral lateral nuclei (Wyder et al., 2003, 2004). The role that neurons in the central thalamus may play in oculomotor control is not yet well understood (Schlag and Schlag-Rey, 1986; Schlag-Rey and Schlag, 1989; Leigh and Zee, 1999).

In recent years, the major focus of studies of the thalamic contribution to eye movement control has been on the role of thalamic nuclei as relay and processing centers in cortical–subcortical–cortical feedback circuits. The most important of these circuits involve feedback from the superior colliculus, basal ganglia, and cerebellum to the cortical eye fields (for review, see Sommer, 2003). These oculomotor feedback loops comprise one case of the general motor and higher-level loops proposed by Alexander et al. (1986, 1990). (See also Chapters 8 and 14.)

The idea of subcortical oculomotor feedback circuits received strong support in the early 1990s when Lynch, Hoover, and Strick used a herpesvirus as a retrograde transneural tracer (Lynch et al., 1994). The virus was placed in the physiologically identified FEFsac in Cebus monkeys. It infected neurons in the thalamus that projected to the FEFsac and then crossed synapses in the thalamus to infect neurons that made synaptic contact with the infected thalamo-cortical neurons. Second-order labeled neurons were observed in the stratum opticum and stratum griseum intermedi-um of the superior colliculus, in pars reticulata of the substantia nigra, and in the dentate nucleus of the cerebellum (Lynch et al., 1994). This study provided confirmation that subcortical structures known to be concerned with oculomotor control had monosynaptic pathways back to the FEFsac, e.g., that the axons of the well-established projection from the superior colliculus to the dorsomedial nucleus of the thalamus (Harting et al., 1980) actually make synaptic contacts with the DM nucleus neurons that project to the FEFsac (Huerta et al., 1986).

A second step in describing possible oculomotor circuits through the thalamus was made when the thalamic input to the FEFsem was found to arise from a different subset of thalamic nuclei than the thalamic input to the FEFsac (and the thalamic input to the SEF was found to differ from that of either the FEFsac or FEFsem) (Tian and Lynch, 1997). In this study, the FEFsac, FEFsem, and SEF were physiologically identified in Cebus monkeys and distinctive retrogradely transported fluorescent tracers were injected into the three regions. Figure 10 illustrates the distribution of neurons that project to the FEFsac (solid dots) and to the FEFsem (open triangles). All labeled neurons were counted in sections spaced at 250-μm intervals through the thalamus (Fig. 11). Neurons labeled by injections in the FEFsac were overwhelmingly concentrated in the paralaminar region of the MD nucleus, a region that receives dense input from the oculomotor layers of the SC (Harting et al., 1980).

In contrast, the majority of neurons that were labeled by the FEFsem injections were located in a variety of thalamic nuclei that received their predominant input from the basal ganglia and cerebellum. These nuclei included VApC and VLcr, targets of the globus pallidus; VAmc, a target of the substantia nigra; and VLcc, a target of the dentate nucleus of the cerebellum. The FEFsem also received input from the MD nucleus, but from a different subregion of the MD than that which projected to the FEFsac. The MD nucleus receives input from the dentate nucleus of the cerebellum (Yamamoto et al., 1992) in addition to its input from the SC.
Fig. 10. The origin of thalamic inputs to the FEFsem (filled circles) and FEFsac (open triangles) in coronal sections of the left hemisphere of a Cebus monkey. Section #1091 is at the most rostral level and section #971 is at the most caudal level. The fluorescent tracers DY and FB were, respectively, injected into the FEFsac and the FEFsem. (See Fig. 16 for injection sites.) A total of 31 sections at 250-μm intervals were plotted. The thalamocortical input to the FEFsem originates predominantly in the ventral lateral, ventral anterior, and mediodorsal nuclei. The thalamocortical input to FEFsac originates overwhelmingly in the paralaminar region of the mediodorsal nucleus. AD, anterior dorsalis; AM, anterior medialis; AV, anterior ventralis; Cd, centralis densocellularis; Cl, centralis lateralis; Csl, centralis superior lateralis; Cn Md, centrum medianum; H, habenula; LD, lateralis dorsalis; LG, lateral geniculate nucleus; Li, nucleus limitans; LP, lateralis posterior; MGmc, medial geniculate nucleus, pars magnocellularis; MGpc, medial geniculate nucleus, pars parvocellularis; MD, medialis dorsalis; MDpc, medialis parvocellularis; MDmc, medialis dorsalis, pars densocellularis; MDmp, medialis dorsalis, pars magnocellularis; MDmf or mf, medialis dorsalis, pars multiformis; MDpc, medialis parvocellularis, pars parvocellularis; Pen, paracentral nucleus; Pf, parafascicularis; Pul O, pulvinaris oralis; Pul L, pulvinaris lateralis; Pul M, pulvinaris medialis; R, reticular nucleus; SG, suprageniculate nucleus; Sm, stria medullaris thalami; VAmc, ventralis anterior, pars magnocellularis; VAp, ventralis anterior, pars parvocellularis; VLc, ventralis lateralis, pars caudalis; VLcc, rostral portion of VLc; VLM, ventralis lateralis, pars medialis; VLo, ventralis lateralis, pars oralis; VLps, ventralis lateralis, pars postrema; VPL, ventralis posterior inferior; VPLc, ventralis posterior lateralis, pars caudalis; VPLo, ventralis posterior lateralis, pars oralis; VPM, ventralis posterior medialis; X, area X in the ventral lateral complex. (Adapted from Fig. 6 of Tian and Lynch, 1997. Copyright 1997, The Society for Neuroscience.)
The pattern of thalamic input to the SEF was different from either the FEFsem or FEFsac, with the majority of input arising from area X, a cerebellar relay nucleus, and from VAp, a relay for the globus pallidus. Injections were also made into the hand/arm region of the dorsal premotor region (PMd) to provide a comparison of the distribution of oculomotor and somatomotor thalamocortical neurons in the VA and VL nuclei. Figure 12 depicts the hypothesized feedback circuits from subcortical oculomotor structures through thalamic nuclei to the FEFsem, FEFsac, and SEF.
The confirmation of one of these proposed cortical–subcortical–cortical feedback loops in the oculomotor system has recently been provided by a series of elegant experiments that combined behavioral neurophysiology and functional neuroanatomy (Sommer and Wurtz, 1998, 2000, 2001, 2004a, b). Sommer and Wurtz first determined the categories of neural information that were sent over the cortico-tectal pathway originating in the FEFsc (Sommer and Wurtz, 2000, 2001). They established that the proportion of movement-, memory-, and vision-related signals that are sent from the FEFsc to the SC are roughly equal to the proportion of such signals observed within the FEFsc (i.e., there is no selection process that increases the proportion of motor-related signals in the FEF-to-SC pathway). Secondly, they established the functional characteristics of the signals that are relayed from the SC back to the FEFsc via the paralaminal region of the MD nucleus. They found that, although visual activity, delay activity, and presaccadic activity are all sent from the SC to the MD nucleus, the delay activity is filtered out of the pathway at the MD nucleus (or perhaps forwarded to a different destination) whereas the visual activity and presaccadic activity is relayed to the FEFsc (Fig. 13). Sommer and Wurtz proposed that the neural signals from the SC to the FEFsc included a corollary discharge that informed the FEFsc of the exact parameters of a just-executed saccadic eye movement (Sommer and Wurtz, 2004a). Finally, Sommer and Wurtz confirmed the corollary discharge nature of the SC-to-MD-to-FEFsc signals by reversibly inactivating the MD relay point and observing a consistent degradation of the accuracy of the second saccade in a double-jump memory saccade paradigm (Sommer and Wurtz, 2002, 2004b).

A similar feedback loop circuit probably exists between the PEF and the SC, although it has not yet been studied in as much detail as the FEF/SC circuit. LIP sends a dense projection to the intermediate layers of the SC (Lynch et al., 1985), and the superficial layers of the SC project back to LIP (Clower et al., 2001), presumably by way of the lateral pulvinar nucleus (Harting et al., 1980; Benevento and Standage, 1983). The neural connections between LIP and SC, therefore, differ from the FEF-to-SC loop. Whereas the information returning to the FEF from the SC is predominantly motor, it appears that the neural information that is transmitted from the SC to LIP is probably visual in nature. As is the case in the FEF-to-SC pathway, the neural signals that are present in the LIP-to-SC pathway are representative of the range of neural

Fig. 12. Summary diagram of GPi/SNr-thalamocortical and cerebellothalamocortical connection patterns. (A) Putative circuits from basal ganglia and cerebellum through thalamic nuclei to the FEFsc and FEFsem. (B) Putative circuits from basal ganglia and cerebellum through thalamic nuclei to the SEF and PMd. Each of the functional areas in the cerebral cortex receives a major neural input from both a basal ganglia-receiving and a cerebellar-receiving cell group in the thalamus. The terms “dorsal” and “ventral,” VLcr and VLcc, emphasize the fact that even though both the FEFsem and the PMd receive input from these two nuclei, the respective pathways originate in separate subregions of these nuclei. Similarly, “dorsal MD” is used to emphasize that the MD projection to the FEFsem originates in the dorsal-most portion of paralaminal MD whereas the MD projection to the FEFsc originates relatively more ventrally in paralaminal MD. VApc, ventralis anterior, pars parvocellularis; VAmc, ventralis anterior, pars magnocellularis; MD, medialis dorsalis; VLcc, caudal portion of ventralis lateralis, pars caudalis; VLcr, rostral portion of ventralis lateralis, pars caudalis; VLO, ventralis lateralis, pars oralis; VPLO, ventralis posterior lateralis, pars oralis; GPi, internal globus pallidus; SNr, substantia nigra, pars reticulata; CBn, cerebellar nuclei; FEFsc, saccadic subregion; FEFsem, smooth eye movement subregion; FEF, frontal eye field; SEF, supplementary eye field; PMd, dorsal premotor cortex. (From Fig. 10 of Tian and Lynch, 1997. Copyright 1997, The Society for Neuroscience.)
Each of the 14 eye fields contribute to this Summary of the cortico-cortical connections among eye fields in the monkey brain. Each cortical eye field has strong reciprocal connections with most or all of the other eye fields. Such connections have been the subject of intense study over the past 20 years. Much is now known about the cortico-cortical connections of the eye fields, their thalamo-cortical connections, and the output connections of the eye fields with subcortical and brainstem structures. A considerable body of evidence now supports the proposal that these cortical areas function together as a cortico-cortical network in controlling voluntary eye movements. Indeed, one of the most striking features of the cortico-cortical connectivity of the cortical eye fields is the degree to which they are connected with each other. Although each eye field has reciprocal connections with sensory and/or limbic association areas, a large proportion of the connectivity of each eye field is with other eye fields. This connectivity is summarized in Fig. 14.

**Frontal eye field**

Perhaps the largest and most important of the connections in this network are those between the FEF and PEF. This connection was first described quantitatively by Barbas and Mesulam (1981), who placed horseradish peroxidase in the region of the low threshold FEF (Case z; “caudal”), then plotted and counted all labeled neurons in every 20th section throughout the brain. The large majority of the cortico-cortical input to the FEF...
originated in visual association areas (53%) and the lateral bank of the intraparietal sulcus (IPS) (23%).

A summary illustration from Barbas and Mesulam (1981) is shown in Fig. 15. Visual association input arose from areas of peristriate cortex (areas 18 and 19 of Brodmann) that include V2, V3, and V4; from inferior temporal cortex (areas 20 and 21 of Brodmann); and from the banks of the superior temporal sulcus (including the locations of areas MT and MST). Additional input came from the region of the SEF, from the prefrontal cortex just anterior to the FEF in the banks of the principal sulcus, and from anterior cingulate cortex. Thus, the cortico-cortical input to the FEF arises from a wide range of visual sensory areas.

Although almost one-fourth of the neuron cell bodies that project to the FEF lie in the lateral bank of the intraparietal sulcus, an area strongly implicated in oculomotor function and visual attention, it should be noted that the majority of the neural input to the FEF originates in visual association areas, and that many of the neurons in the FEF have activity related to visual stimuli.

Andersen et al. (1985) confirmed the relationship between the FEF and the lateral bank of the intraparietal sulcus, and named the lateral bank cortex the “lateral intraparietal area” (LIP). He demonstrated that LIP sends a dense projection to the anterior bank of the arcuate sulcus (FEF), whereas the cortex of the convexity of the inferior parietal lobule, area 7a, had only modest connections to the FEF but projected densely to area 46 in the banks of the principal sulcus. The specifically oculomotor connections of LIP were also emphasized by Lynch and Graybiel, who demonstrated that LIP, but not adjacent area 7a, sends a dense projection selectively to the intermediate, oculomotor-related, layers of the superior colliculus (Lynch et al., 1985).

It is often assumed that the predominant flow of information in the cortical oculomotor system is from occipital, parietal, and temporal areas toward the FEF and thence to the brainstem. However, there is also a significant flow of information in the opposite direction, from the FEF back to the visual association areas, which is probably of equal magnitude. The reciprocal nature of most of the cortico-cortical connections of the FEF were first described in detail by Huerta et al. (1987), who used both anterograde and retrograde tracers in the same monkeys. The importance of the neural connections from the FEF back to the visual association cortex has recently been emphasized by a study that demonstrated electrical microstimulation in the FEF could modulate the activity of neurons in V4 (Moore and Armstrong, 2003).

The general results of Huerta’s study (Huerta et al., 1987) were very similar to those of Barbas (Barbas and Mesulam, 1981), although Huerta described a stronger connection with the SEF than did Barbas, and did not observe such a large connection with visual association cortex as did Barbas (see Figs. 4 and 6 in Huerta et al., 1987). In addition to the basic information about the cortical connections of the FEF, these figures illustrate an important principle of cortico-cortical connectivity: The connections between cortical areas are not as precise as the electrical connections inside a computer or television set. There are differences between the results of different investigators and there are differences between different subjects in a single investigation that can only be partially accounted for by differences in methodology or differences in the exact placement of tracers (see, e.g., Stanton et al., 1995). There are undoubtedly differences in the details of neural wiring diagrams from one individual to another. Although block diagrams can provide a useful way to simplify overwhelmingly complex connectional information, it is important to keep in mind the neuroanatomical data underlying the block diagrams when formulating hypotheses about the function of the oculomotor system.

The topographical details of several cortico-cortical connections of the FEF have recently been studied in detail. In general, the more lateral portion of the FEF, that which is concerned with small amplitude saccades, is predominantly connected with the foveal representations of retinotopically organized association cortex regions and with areas that primarily represent central vision. The more medial portion of the FEF, which is concerned with large amplitude saccades, is connected predominantly with the peripheral retinal representations in cortical regions that are
In addition to its connections with other eye fields, the FEF receives direct neural input from many visual association areas. The quantitative distribution of afferent cortico-cortical input to the FEF of the macaque monkey is illustrated in medial (1), lateral (2), and inferior (3) views of the brain. The dark area at the posterior tip of the principal sulcus (P) indicates the site of HRP injection. Retrogradely labeled neurons were counted in representative sections (usually every other section) throughout the brain. The density of the black diamonds is proportional to the distribution of the labeled neurons. Solid lines indicate the fundi of sulci; dashed lines indicate the banks of the sulci. A, arcuate sulcus; C, central sulcus; Ca, calcarine sulcus; Cg, cingulate sulcus; IO, inferior occipital sulcus; IP, intraparietal sulcus; L, lunate sulcus; LF, lateral fissure; MPO, medial parieto-occipital sulcus; OP, parieto-occipital sulcus; P, principal sulcus; PMT, posterior middle temporal sulcus; ST, superior temporal sulcus. (From Fig. 3 of Barbas and Mesulam, 1981.)
retinotopically organized and with association areas in which peripheral vision is emphasized (Stanton et al., 1993, 1995; Schall et al., 1995; for review, see Schall, 1997).

The connections between the FEF and the SEF have been described in considerable detail, although it is more difficult to establish a precise topographical relationship because of the very small size of the SEF. Nevertheless, it is clear that the largest portion of the SEF projects to the region of the FEF concerned with intermediate amplitude saccades. Furthermore, those parts of the SEF that project to the small amplitude part of the FEF also project to the large amplitude part of the FEF (Schall et al., 1993). Therefore, there is some crude topography in these connections, but nothing approaching the elegant retinotopic representations that are present in striate and prestriate cortex.

Most recently, the distinct afferent connections of the FEFsac and FEFsem have been described and compared in a series of studies by Tian and Lynch (1996a, b, 1997). Small injections of retrogradely transported tracers were placed in the physiologically identified saccade subregion of the FEF (FEFsac) and in the pursuit subregion (FEFsem). A summary of the major cortico-cortical afferent connections of these two regions is shown in Fig. 16. The location of neurons projecting to the FEFsac is indicated by open triangles in Fig. 16; the location of neurons projecting to the FEFsem are indicated by closed circles. The cortico-cortical input to the FEFsac in Cebus monkeys corresponded closely to that which has previously been described in macaque monkey.

The FEFsac received a large input from the PEF. An interesting feature of this connection is that a single, small injection in the FEFsac resulted in labeled neurons over most of LIP and adjacent VIP (see Fig. 4, Tian and Lynch, 1996b). This observation indicates considerable convergence in the LIP-to-FEFsac pathway. Neurons labeled by the FEFsac injection were also observed in the prefrontal cortex in and along the banks of the principal sulcus (PFEF), the SEF, the MST area, and the DM area. The FEFsem also had afferent connections with the PEF, PFEF, SEF, and MST, but in each of these areas the neuron cell bodies that projected to the FEFsem were located within a region that was separate from but adjacent to the region containing cell bodies that projected to the FEFsac. The FEFsem also received a strong afferent projection from a parietal region on the medial wall of the hemisphere that was within area 7m. These observations led Tian and Lynch to propose that there are two parallel cortico-cortical networks related to oculomotor control: one devoted primarily to saccadic eye movements and one devoted primarily to pursuit eye movements (see also Fig. 18).

**Parietal eye field**

The major afferent and efferent corticocortical connections of the PEF were described in detail by Cavada and Goldman-Rakic (1989a, 1989b) and are illustrated in Fig. 17. In addition to its massive reciprocal connection with the FEF that is described above, the PEF (which includes LIP but extends beyond it medially) has reciprocal connections with two other oculomotor-related regions in the frontal lobe, the SEF and the posterior part of area 46 (the PFEF) (Cavada and Goldman-Rakic, 1989b; Andersen et al., 1990a; Blatt et al., 1990). The PEF is also connected with oculomotor-related regions in the parietal and temporal lobes: MST and 7m (Cavada and Goldman-Rakic, 1989a; Andersen et al., 1990a; Blatt et al., 1990). The PEF has numerous connections with visual association areas in prestriate and temporal cortex, including V2, V3, and V4 in Brodmann’s areas 18 and 19; the middle temporal area (MT); the superior temporal polysensory area (STP); inferotemporal cortex (TEa, TEM, and TEO); the parieto-occipital visual area (PO); the dorsal prelunate area (DP); and the lateral posterior parahippocampal gyrus (TF) (Cavada and Goldman-Rakic, 1989a; Andersen et al., 1990a; Blatt et al., 1990). It is important to note that almost all of these connections are reciprocal. Furthermore, almost all of the visual association areas that project to the PEF also project directly to the FEF. This feature of connectivity is an argument in favor of a parallel position of the FEF and PEF in oculomotor processing (Fig. 18).
Supplementary eye field

The neural connections of the SEF are similar to those of the FEF, but the SEF does not have connections with as many visual association areas, nor are the existing connections with association areas as strong as those of the FEF (for reviews, see Schall, 1997; Tehovnik et al., 2000). The densest connections of the SEF are with the FEF (Huerta et al., 1987; Huerta and Kaas, 1990; Stanton et al., 1993; Schall et al., 1993). There is some topography evident in these connections. The FEFsac and
the FEFsem are connected to spatially distinct subregions of the SEF (Tian and Lynch, 1996b), and the SEF projects predominantly to that part of the FEF concerned with saccades of intermediate amplitude (Schall et al., 1993) (see discussion of FEF connections, above). The SEF has reciprocal connections with the PFEF (Huerta and Kaas, 1990); with LIP (Huerta and Kaas, 1990; Schall et al., 1995); with 7a (Huerta and Kaas, 1990); and receives afferent input from MST and the STP (Huerta and Kaas, 1990). In addition, SEF is reciprocally connected with several somatomotor areas, including the SMA, the dorsal premotor area, and the rostral and caudal cingulate motor areas (CMAr and CMAc) (Huerta and Kaas, 1990). These cingulate areas have

Fig. 17. LIP is reciprocally connected with many of the same visual association areas that are connected with the FEF, in addition to the connections of LIP with other eye fields (compare this figure with Fig. 15). The distribution of retrogradely labeled neurons cell bodies and anterogradely labeled axon terminals following injections of tracers into area LIP (dark gray region in the posterior bank of the IP sulcus) in a macaque monkey are illustrated in this figure. Large dots indicate concentrations of labeled neuron cell bodies; small dots indicate distribution of labeled axon terminals. A, arcuate sulcus; C, central sulcus; Ca, calcarine sulcus; Ci, cingulate sulcus; IP, intraparietal sulcus; L, lunate sulcus; LF, lateral fissure; P, principal sulcus; ST, superior temporal sulcus. (Adapted from Fig. 14 of Cavada and Goldman-Rakic, 1989a, and Fig. 10 of Cavada and Goldman-Rakic, 1989b.)
recently been implicated in oculomotor control by an fMRI study (Berman et al., 1999).

**Medial superior temporal area**

The MST receives a large input from area MT, an area specialized for the analysis of the velocity of moving visual stimuli, and projects back to MT (Tusa and Ungerleider, 1988; Boussaoud et al., 1992). It is also reciprocally connected to visual areas V2, V3a, and PO; the fundus of the superior temporal sulcus (area FST); and parietal areas LIP, VIP, and 7a. MST is also connected with both the pursuit and saccade subregions of the FEF, and the cortex of the principal sulcus (Tusa and Ungerleider, 1988; Boussaoud et al., 1990; Tian and Lynch, 1996b; Maioli et al., 1998).

**Prefrontal eye field**

The dorsolateral prefrontal cortex, in and around the banks of the principal sulcus in monkeys, is connected to other eye fields, to visual association areas, and to limbic structures (for reviews, see Goldman-Rakic, 1987; Selemon and Goldman-Rakic, 1988). The PFEF has dense reciprocal connections with the FEF (Barbas and Mesulam, 1985; Huerta et al., 1987). The FEFsac is more heavily connected with cortex in the fundus of the principal sulcus and with the inferior shoulder of the sulcus, whereas the FEFsem is more heavily connected with the cortex of the superior shoulder of the sulcus and the adjacent cortex of the hemispheric convexity (Tian and Lynch, 1996b). The SEF has reciprocal connections with the PFEF (Huerta and Kaas, 1990), as does area 7m (Cavada and Goldman-Rakic, 1989b). The PFEF is interconnected with both the LIP and area 7a, but more densely connected with 7a than with LIP (Andersen et al., 1985, 1990a; Barbas and Mesulam, 1985; Cavada and Goldman-Rakic, 1989b; Blatt et al., 1990). Finally, the PFEF has connections to orbital prefrontal cortex (Barbas and Mesulam, 1985), the superior temporal gyrus (Barbas and Mesulam, 1985), and the parahippocampal gyrus (Goldman-Rakic et al., 1984).
Precuneus (area 7m)

Tian and Lynch (1996b) observed a large, dense cluster of labeled neurons in the parietal lobe on the medial wall of the hemisphere following injections of retrogradely transported tracers in FEFsem (see Fig. 16), but only a few labeled neurons in this region following injections in FEFsa. The region was about half-way between the calcarine sulcus and the shoulder of the hemisphere, at the anterior–posterior level of the posterior half of the intraparietal sulcus, within the area commonly designated cytoarchitectural area 7m (Cavada and Goldman-Rakic, 1989a, b). Area 7m has been implicated in oculomotor control (Thier and Andersen, 1998; Petit and Haxby, 1999) and hand–eye coordination (Ferraina et al., 1997a, b; Meister et al., 2004).

In addition to the strong connection to the FEFsem, area 7m is connected with the SEF, the PFEF, dorsal premotor cortex (PMd), and the supplementary motor area (SMA) in the frontal lobe (Cavada and Goldman-Rakic, 1989b; Leichnetz, 2001). In the parietal and temporal lobes, area 7m is connected with LIP, MST, MT, V2, and PO, to area 5 (a somatosensory association area), the supplementary somatosensory area (SSA), and posterior cingulate cortex (Cavada and Goldman-Rakic, 1989a; Leichnetz, 2001).

Summary

Current evidence strongly supports the proposal that there are multiple distinct regions in the cerebral cortex that make direct contributions to the initiation and control of voluntary eye movements. Six of these regions have here been discussed in some detail: FEF, PEF, SEF, MST, PFEF, and 7m. Each of these regions has neural activity closely related to eye movements; electrical microstimulation within each region produces or modifies eye movements; surgical lesions or chemical inactivation of each region produces impairments of eye movements; each region has direct neural projections to major structures in the brainstem oculomotor system; and each region demonstrates increased activity during eye movement tasks in fMRI experiments in humans.

The cortico-cortical connectivity of these eye fields is summarized in Fig. 18. Each of the eye fields is connected to most or all of the other eye fields. This connectivity is reciprocal, with much neural information going in each direction, and most of the eye fields receive direct input from several regions of visual association cortex. Moreover, recent studies by Tian and Lynch demonstrated that the pursuit subregion of the frontal eye field (FEFsem) and the saccade subregion of the frontal eye field (FEFsa) are selectively connected with distinct subregions in each of the other eye fields. They, therefore, proposed that there are two parallel cortical oculomotor networks, one devoted to primarily to the control of pursuit eye movements and a second devoted primarily to the control of saccadic eye movements (Tian and Lynch, 1996b).

The proposal of distributed cortical oculomotor networks is supported by lesion and inactivation experiments. Damage or inactivation of single nodes in the network (either the FEF or PEF) produces measurable impairment of oculomotor control, but recovery is rapid, typically almost complete within a few days. In contrast, when two nodes are damaged simultaneously (e.g., the FEF and PEF together), the oculomotor impairment is much more severe and lasts much longer (Lynch, 1992). Furthermore, the suggestion of two parallel cortico-cortical networks has received direct support from a recent fMRI study by Petit and Haxby, which demonstrated simultaneous activation in the FEF, PEF, SEF, MT/MST region, and precuneus (7m) regions during saccadic eye movement tasks and activation of adjacent but not totally overlapping portions of each of these eye fields during visual pursuit tasks (Petit et al., 1997; Petit and Haxby, 1999).

Finally, numerous recent publications have presented evidence that supports the proposal that distributed cortico-cortical networks play a critical role in the control of voluntary eye movements, shifts of visual attention, and related neural processes (Corbetta, 1998; Corbetta et al., 1998; Berman et al., 1999; Compte et al., 2000; Haxby et al., 2000; Ishai et al., 2000; Munoz, 2002; Astafiev et al., 2003; d’Avossa et al., 2003; Krauzlis, 2004).
We are now poised to make rapid progress in understanding the higher neural control of voluntary eye movements. Advances in the transsynaptic tracing of neural pathways are leading to a much clearer understanding of the neural circuitry of the oculomotor system. The combination of single-neuron recording and antidromic electrical stimulation in behaving nonhuman primates has opened a new field, which might be called “physiological anatomy.” Although each of these techniques has been in use for many years, the recent ability of investigators to use all three together now enables neuroscientists not only to specify what types of neural activity are present in a given region of the nervous system, but also to determine which type of activity is transmitted along particular anatomically defined pathways to particular efferent targets of the original structure. This ability provides an enormous increment in our ability to understand the nervous system “in terms of information processing functions and systems.” Finally, the steadily increasing sophistication of functional imaging studies will allow the direct testing, in humans, of hypotheses developed in animal studies and will also provide the stimulation for new approaches in animal studies based on information gained in functional imaging studies in humans.

**Abbreviations**

**Cerebral Cortex**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>arcuate sulcus</td>
</tr>
<tr>
<td>AS</td>
<td>arcuate spur</td>
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<tr>
<td>C</td>
<td>central sulcus</td>
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<tr>
<td>Ca</td>
<td>calcarine sulcus</td>
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<tr>
<td>Ci, Cg</td>
<td>cingulate sulcus</td>
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<tr>
<td>Cl</td>
<td>claustrum</td>
</tr>
<tr>
<td>FEF</td>
<td>frontal eye field</td>
</tr>
<tr>
<td>FEFsac</td>
<td>saccadic subregion of the FEF</td>
</tr>
<tr>
<td>FEFsem</td>
<td>smooth eye movement subregion of the FEF</td>
</tr>
<tr>
<td>IA</td>
<td>inferior arcuate sulcus</td>
</tr>
<tr>
<td>IO</td>
<td>inferior occipital sulcus</td>
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<tr>
<td>IP, IPS</td>
<td>intraparietal sulcus</td>
</tr>
<tr>
<td>L</td>
<td>lunate sulcus</td>
</tr>
<tr>
<td>LF</td>
<td>lateral fissure</td>
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<tr>
<td>LIP</td>
<td>lateral intraparietal area</td>
</tr>
<tr>
<td>MPO</td>
<td>medial parieto-occipital sulcus</td>
</tr>
<tr>
<td>MST</td>
<td>medial superior temporal area</td>
</tr>
<tr>
<td>Or</td>
<td>orbital sulcus</td>
</tr>
<tr>
<td>OP</td>
<td>parieto-occipital sulcus</td>
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<tr>
<td>OT</td>
<td>occipitotemporal sulcus</td>
</tr>
<tr>
<td>P</td>
<td>principal sulcus</td>
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<tr>
<td>PEF</td>
<td>parietal eye field</td>
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<tr>
<td>PFEF</td>
<td>prefrontal eye field</td>
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<tr>
<td>PMd</td>
<td>dorsal premotor area</td>
</tr>
<tr>
<td>PMr</td>
<td>rostral premotor area</td>
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<tr>
<td>PMT</td>
<td>posterior middle temporal sulcus</td>
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<tr>
<td>PMv</td>
<td>ventral premotor area</td>
</tr>
<tr>
<td>PO</td>
<td>parieto-occipital sulcus</td>
</tr>
<tr>
<td>SA</td>
<td>superior arcuate sulcus</td>
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<tr>
<td>SAC</td>
<td>saccadic eye movement subregion of FEF</td>
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<tr>
<td>SEF</td>
<td>supplementary eye field</td>
</tr>
<tr>
<td>SEM</td>
<td>smooth eye movement subregion of FEF</td>
</tr>
<tr>
<td>ST, STS</td>
<td>superior temporal sulcus</td>
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**Subcortical**

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<tr>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>AD</td>
<td>nucleus anterior dorsalis</td>
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<tr>
<td>AM</td>
<td>nucleus anterior medialis</td>
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<tr>
<td>APN</td>
<td>anterior pretectal nucleus</td>
</tr>
<tr>
<td>AV</td>
<td>nucleus anterior ventralis</td>
</tr>
<tr>
<td>BP</td>
<td>brachium pontis</td>
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<tr>
<td>ChN</td>
<td>cerebellar nuclei</td>
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<tr>
<td>Cdc</td>
<td>nucleus centralis densocellularis</td>
</tr>
<tr>
<td>CG</td>
<td>central gray</td>
</tr>
<tr>
<td>Cl</td>
<td>central lateral nucleus</td>
</tr>
<tr>
<td>Cn Md, CM</td>
<td>nucleus centrum medianum</td>
</tr>
<tr>
<td>CP</td>
<td>cerebral peduncle</td>
</tr>
<tr>
<td>CS</td>
<td>central superior nucleus of the raphe</td>
</tr>
<tr>
<td>Csl</td>
<td>nucleus centralis superior lateralis</td>
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<tr>
<td>Cun</td>
<td>cuneiform nucleus</td>
</tr>
<tr>
<td>DBC</td>
<td>decussation of the brachium conjunctivum</td>
</tr>
<tr>
<td>DLG</td>
<td>dorsal lateral geniculate nucleus</td>
</tr>
<tr>
<td>DLPN</td>
<td>dorsolateral pontine nuclei</td>
</tr>
<tr>
<td>DMPN</td>
<td>dorsomedial pontine nuclei</td>
</tr>
<tr>
<td>Fx</td>
<td>fornix</td>
</tr>
<tr>
<td>GP</td>
<td>globus pallidus</td>
</tr>
<tr>
<td>Gpi</td>
<td>internal segment of globus pallidus</td>
</tr>
<tr>
<td>H, Hb</td>
<td>habenula</td>
</tr>
<tr>
<td>I Pul</td>
<td>inferior pulvinar</td>
</tr>
<tr>
<td>IC</td>
<td>inferior colliculus</td>
</tr>
<tr>
<td>INC</td>
<td>interstitial nucleus of Cajal</td>
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<td>Term</td>
<td>Definition</td>
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<tr>
<td>L Pul</td>
<td>nucleus pulvinaris lateralis</td>
</tr>
<tr>
<td>LD</td>
<td>nucleus lateralis dorsalis</td>
</tr>
<tr>
<td>LG</td>
<td>lateral geniculate nucleus</td>
</tr>
<tr>
<td>Li</td>
<td>nucleus limitans</td>
</tr>
<tr>
<td>LLd</td>
<td>dorsal nucleus of the lateral lemniscus</td>
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